



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁴ : C08G 18/77, A61L 15/01, 27/00 A61F 2/06	A1	(11) International Publication Number: WO 89/ 05830 (43) International Publication Date: 29 June 1989 (29.06.89)
(21) International Application Number: PCT/NL88/00060 (22) International Filing Date: 22 December 1988 (22.12.88) (31) Priority Application Number: 8703115 (32) Priority Date: 23 December 1987 (23.12.87) (33) Priority Country: NL (71) Applicant (for all designated States except US): STICHTING BIOMAT [NL/NL]; Zernike Park 2, NL-9747 AN Groningen (NL). (72) Inventor; and (75) Inventor/Applicant (for US only) : PENNING, Albert, Johan [NL/NL]; Ettenlaan 3, NL-9331 BE Norg (NL). (74) Agent: SMULDERS, Th., A., H., J.; Vereenigde Octro- oibureaux, Nieuwe Parklaan 107, NL-2587 BP The Hague (NL).		(81) Designated States: AT (European patent), BE (Euro- pean patent), CH (European patent), DE (European patent), FR (European patent), GB (European pa- tent), IT (European patent), JP, LU (European pa- tent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>
(54) Title: BIODEGRADABLE POLYURETHANES, PRODUCTS BASED THEREON, AND POLYESTER POLYOL PREPOLYMERS (57) Abstract This invention relates to biodegradable polyurethanes on the basis of a polyol prepolymer and an L-lysine derivative having at least 2 isocyanate groups. The polyol prepolymer is preferably a polyester polyol prepolymer obtained by ring-opening polymerization of L-lactide, glycolide and/or lactone with a cyclic polyol. These new polyurethanes can be used in the production of different types of biomedical products, such as artificial skin, wound dressing, artificial veins, nerve grafts etc.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	ML	Mali
AU	Australia	GA	Gabon	MR	Mauritania
BB	Barbados	GB	United Kingdom	MW	Malawi
BE	Belgium	HU	Hungary	NL	Netherlands
BG	Bulgaria	IT	Italy	NO	Norway
BJ	Benin	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	LI	Liechtenstein	SN	Senegal
CH	Switzerland	LK	Sri Lanka	SU	Soviet Union
CM	Cameroon	LU	Luxembourg	TD	Chad
DE	Germany, Federal Republic of	MC	Monaco	TG	Togo
DK	Denmark	MG	Madagascar	US	United States of America
FI	Finland				

Title: Biodegradable polyurethanes, products based thereon,
and polyester polyol prepolymers

This invention relates to a biodegradable polyurethane
on the basis of a polyol prepolymer and a polyisocyanate.

The invention further relates to products, especially
biomedical products, such as artificial skin, wound
5 dressings, artificial veins, vein grafts, nerve grafts,
etc., comprising such a polyurethane.

Furthermore, the invention relates to a polyester
polyol prepolymer adapted for use in the preparation
of the polyurethane.

10 Polyurethanes are considered to be excellent biomedical
materials having good mechanical and physical properties
and showing a satisfactory blood compatibility. For
these reasons linear (thermoplastic) elastomeric polyurethanes
are used, e.g., in biodegradable polyurethanes/poly(L-lactide)
15 blends for the production of biomedical products, such
as grafts for blood vessels, meniscus prostheses, artificial
skin products and nerve grafts. See, e.g., Gogolewski
and Pennings, Makromol. Chem., Rapid Commun. 3 (1982)
839 and 4 (1983) 675.

20 The prior art polyurethane/poly(L-lactide) compositions,
however, show in vivo, after initial fragmentation,
a very low rate of degradation. Besides, dynamic load

-2-

will give rise to creep conditions leading to aneurysms in grafts for blood vessels. An even more important disadvantage of the polyurethane elastomers known for biomedical uses with biodegradation, such as Biomer, Estane, etc., is that toxic, mutagenic and carcinogenic substances, such as 4,4'-methylenedianiline when the polyurethane has been prepared using 4,4'-methylene diphenyl diisocyanate, may be released upon degradation. It is well-known that this disadvantage can be mitigated by using non-aromatic polyisocyanates in the preparation of the polyurethanes. Szycher et al., J. Elastomers and Plastics 15 (1983) 81-95, for instance, propose to use cycloaliphatic diisocyanates, such as 4,4'-methylene-bis-cyclohexyl diisocyanate. Reaction of this diisocyanate with a polytetramethylene ether glycol (having a molecular weight of about 1000) and 1,4-butanediol gives biomedical grade cycloaliphatic polyurethane elastomers sold under the trade name Tecoflex. It has also been proposed to use non-cyclic aliphatic polyisocyanates, such as 1,6-hexane diisocyanate, in the preparation of polyurethane. The corresponding diamines that may be released upon degradation of the polyurethanes, however, are more or less still toxic.

With regard to the polyols to be used in the preparation of polyurethanes, it is known to use polyester polyol prepolymers for this purpose. Thus, for instance, Schindler et al., J. Polym. Sci. 20 (1982) 319 describe the forming of stellate polycaprolactone polymers by

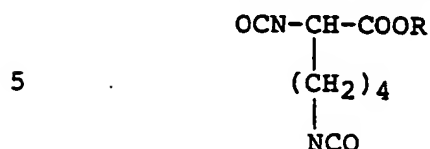
an alcohol-initiated ring-opening polymerization of ϵ -caprolactone, the alcohol used being a cyclic sugar, such as sorbitol, xylitol or ribitol. Pitt et al., J. Polym. Sci. 25 (1987) 955 describe the preparation of biodegradable polyurethanes from prepolymers having 3 terminal hydroxyl groups obtained by a glycerol-initiated ring-opening copolymerization of a 1 : 1 mixture of δ -valerolactone and ϵ -caprolactone. These prepolymers are crosslinked with 1,6-hexane diisocyanate.

Furthermore, Schindler et al., in "Cont. Topics in Polym. Sci." (Eds. Pearce and Schaeffgen) Plenum Press N.Y., USA, vol. 2 (1977) and Kricheldorf et al., Macromolecules 17 (1984) 2173 already describe biodegradable copolyesters of L-lactide or glycolide and ϵ -caprolactone.

However, biodegradable polyurethane elastomers having a combination of properties suitable for different biomedical uses and especially giving no toxic degradation products upon degradation have not been described so far.

This invention provides a biodegradable polyurethane on the basis of a polyol prepolymer and a polyisocyanate which satisfies this need and is characterized in that the polyisocyanate is an L-lysine derivative having at least 2 isocyanate groups. More in particular, this invention relates to such a biodegradable polyurethane in which the polyol prepolymer is a polyester polyol prepolymer.

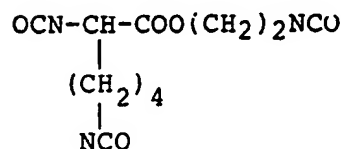
The L-lysine derivative to be used according to the invention in the preparation of the polyurethane is preferably a compound having the structural formula .



in which R is an alkyl-, aryl-, alkaryl- or aralkyl group, which may be substituted by one or more isocyanate groups and/or groups inert in the polyurethane-forming reaction, such as alkoxy groups. It is preferred that R is a lower alkyl group, most preferably the ethyl group, and that this lower alkyl group is not substituted or substituted by an isocyanate group.

Such L-lysine polyisocyanates are known per se from French patent 1,351,368, which also describes their preparation and their usability in the preparation of polyurethane foams, adhesives and elastomers. This publication, however, in no way suggests the conversion of such L-lysine polyisocyanates with polyol prepolymers, especially polyester polyol prepolymers, to biomedically applicable polyurethanes.

The polyurethane according to the invention may be based on a polyester diol prepolymer and an L-lysine derivative having at least 3 isocyanate groups, preferably L-lysine aminoethyl ester triisocyanate having the structural formula

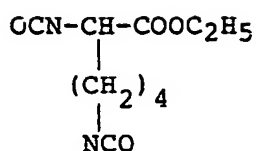


The polyester diol prepolymer is preferably a prepolymer
5 obtained by a ring-opening polymerization reaction of
L-lactide, glycolide and/or one or more lactones, such
as ϵ -caprolactone and δ -valerolactone, if desired initiated
with a diol, such as glycol, 1,4-butanediol, 1,6-hexanediol,
etc. Most preferably, a prepolymer is obtained by a
10 ring-opening copolymerization, if desired initiated
with a diol, of L-lactide and/or glycolide with one
or more lactones, such as ϵ -caprolactone and δ -valerolactone.

The invention, however, also comprises linear or
non-linear biodegradable polyurethanes based on an L-lysine
15 derivative having 2 or more isocyanate groups, such
as L-lysine ethyl ester diisocyanate and L-lysine aminoethyl
ester triisocyanate; a diol prepolymer, e.g., a polyether
diol, such as polytetramethylene glycol having a molecular
weight of about 1000-2000, or a polyester diol, such
20 as polycaprolactone diol having a molecular weight of
about 1000-2000; and a chain extender, such as 1,4-butane
diol.

The polyurethane according to the invention is,
however, preferably based on an L-lysine diisocyanate,
25 most preferably L-lysine ethyl ester diisocyanate having
the structural formula

-6-



and a polyester polyol prepolymer having at least 3
5 hydroxyl groups. This polymer is preferably obtained
by a ring-opening polymerization reaction of L-lactide,
glycolide, and/or one or more lactones, such as ϵ -capro-
lactone and δ -valerolactone, with a polyol containing
at least 3 hydroxyl groups. In this case, too, a copoly-
10 merization of L-lactide and/or glycolide with one or
more lactones, such as ϵ -caprolactone and δ -valerolactone,
is preferred. The polyol to be used to initiate the
polymerization reaction is preferably a cyclic polyol
and in particular myo-inositol has proved to be eminently
15 suited for this purpose, in relation to the contemplated
uses of the polyurethane.

Most preferred is a polyurethane according to the
invention, in which the polyester polyol prepolymer
is obtained by a ring-opening polymerization reaction
20 of L-lactide or glycolide with ϵ -caprolactone and with
myo-inositol, and the L-lysine polyisocyanate is the
compound L-lysine ethyl ester diisocyanate. The monomeric
products that may be released upon full degradation
of such a polyurethane are myo-inositol (a vitamin occurring
25 in human beings), L-lactic acid or glycolic acid, 6-hydroxy-
hexanoic acid, L-lysine and ethanol. These monomeric
compounds are all non-toxic, which is of great importance

-7-

to the use of the polyurethane as a degradable biomedical material. The second advantage due to the use of L-lysine ethyl ester diisocyanate is that the carboxyl group formed in the hydrolysis of the ethyl ester has a catalytic effect on the further degradation of the polymer. The advantage of L-lactide (or glycolide)/ ϵ -caprolactone copolyester prepolymers is that the polyurethanes based thereon combine good elastomeric properties with a high rate of biodegradation. Polyurethanes on the basis of L-lactide/myo-inositol or glycolide/myo-inositol prepolymers have glass transition temperatures (T_g) above room temperature, while polyurethanes on the basis of poly(ϵ -caprolactone) prepolymers have a low rate of biodegradation, which is undesirable for many uses. The polyurethanes preferred according to the invention on the basis of copolyester prepolymers preferably containing approximately equimolar amounts of L-lactide (or glycolide) and ϵ -caprolactone combine low glass transition temperatures, e.g., within the range of 0-10°C, with a relatively high rate of biodegradation. The glass transition temperature can be adjusted to a desired value by controlling the chain lengths of the copolyester prepolymers; greater chain lengths lead to lower values of the glass transition temperature. In this connection the fact is to be considered that residues of non-reacted monomers and oligomers show a plasticizer effect, so that an extraction treatment of the polymer, e.g., with chloroform, as a result of

the removal of such monomers and oligomers, will lead to a somewhat higher glass transition temperature.

These residues of monomers and oligomers also affect the gel content of the polyurethanes according to the invention. The highest gel contents are obtained when the prepolymer, prior to its reaction with the L-lysine polysocyanate, is liberated from such low molecular residues by precipitating the prepolymer by means of a non-solvent, such as ethanol, from a solution of the prepolymer in an organic solvent, such as chloroform. Higher gel contents can also be obtained by using a slight excess of the isocyanate groups over the hydroxyl groups. Besides forming urethane links, an additional crosslinking may occur by means of forming allophanate groups.

In connection with different biomedical uses, e.g., as a base for artificial skin products for covering wounds (burns), or as an internal layer of blood vessel and nerve grafts, the polyurethane according to the invention preferably consists of a porous network. Such a porous polyurethane network is obtainable by carrying out the reaction between polyester polyol prepolymer and L-lysine polyisocyanate in the presence of a salt, such as sodium chloride, and removing this salt later, e.g., by treatment with water, whereby pores remain.

This invention also comprises products which completely or partly consist of a polyurethane according to the

invention, in particular sheet-like biomedical products, such as artificial skin, wound dressings etc. and tubular biomedical products, such as artificial veins, vein grafts, nerve grafts etc. Furthermore, the polyurethanes according to the invention can also be used as a biodegradable carrier for medicaments etc., as a (component of) biodegradable suture, etc.

The invention also extends to a polyester polyol prepolymer on the basis of (1) a cyclic polyhydroxy compound having at least 3 functional hydroxyl groups, (2) L-lactide and/or glycolide, and (3) one or more lactones, such as ϵ -caprolactone and δ -valerolactone, especially to such a prepolymer in which the polyhydroxy compound is myo-inositol and/or the lactone is ϵ -caprolactone.

An example serves to illustrate the invention.

Example

(a) Preparation of the prepolymers

L-lactide (sold by C.C.A., Gorinchem, The Netherlands; after recrystallization from dry toluene) or glycolide (sold by Dupont), as well as ϵ -caprolactone (sold by Janssen Chemical, Belgium; after distillation) and myo-inositol (sold by Merck) were dissolved in dry dimethylformamide at 140°C. As a catalyst 0.5 % by weight of tin(II)octoate (sold by Sigma Chem. Corp. USA) were

-10-

added, and the polymerization was carried out for 20 hours at 120-130°C under a nitrogen atmosphere. After removal of the solvent under reduced pressure a sticky, yellowish prepolymer remained. A part of this prepolymer was precipitated in ethanol (-70°C) from a solution in chloroform and dried at room temperature under reduced pressure.

(b) Preparation of L-lysine ethyl ester diisocyanate

L-lysine monohydrochloride (sold by Janssen Chemical, Belgium) was converted to L-lysine ethyl ester dihydrochloride by boiling in ethanol under conditions of reflux while passing HCl gas through the solution. By phosgenating this L-lysine ethyl ester dihydrochloride in ortho-dichlorobenzene for about 8 hours at 100-110°C L-lysine ethyl ester diisocyanate was obtained which was purified by vacuum distillation (boiling point 125°C at 0.1 mm Hg).

(c) Forming of the polyurethane network

L-lactide/ ϵ -caprolactone copolyester prepolymers were crosslinked by treatment with L-lysine ethyl ester diisocyanate in toluene. The crosslinking of glycolide/ ϵ -caprolactone copolyester prepolymers was carried out in dichloromethane. The molar ratio of hydroxyl groups to isocyanate groups was 1. By a one-day reaction at

-11-

room temperature under nitrogen in a Petri dish and a three-hour rehardening at 100-110°C thin films were obtained. The elastic, transparent films were dried at 50°C under reduced pressure.

Porous films having a pore volume of about 85 % are obtained by hardening a viscous suspension of prepolymer, diisocyanate, solvent and an amount of dry NaCl powder having a variable particle size and removing the salt by washing the NaCl polymer blend with water, in the manner as indicated above.

(d) Results

The gel contents(% w/w) were determined by extracting the networks with chloroform. The extracted networks were dried for some days at 50°C under reduced pressure.

Swelling tests were carried out at the extracted networks at room temperature in chloroform. The degree of swelling was calculated from the increase in weight after swelling, using the densities of chloroform ($\rho = 1.48 \text{ g/cm}^3$) and the dry extracted networks ($\rho = 0.90 - 0.95 \text{ g/cm}^3$).

A thermal analysis of the networks was carried out by means of a Perkin-Elmer DSC-7, which was calibrated with reference materials certified by the I.C.T.A. (International Confederation for Thermal Analysis) and was used at a scanning rate of 10°C/min.

Mechanical properties were determined at room temperature by means of an Instron (4301) tensile strength tester provided with a 10N load cell, at a drawing speed of 12 mm/min. For this purpose, samples of 15 x about 0.75 x about 0.25 mm were cut from extracted or unextracted thin films.

For the porous materials the microstructure was examined by means of an I.S.I.-DS130 scanning electron microscope.

The results of the above-described examinations, with the exception of the electron microscopic examination, are listed in the following Table.

Polyester urethane network data

polyurethane network ^{a)}	prepolymer chain length ^{b)}	T _g (°C)	gel content (%)	elongation at break	tensile strength (MPa)	degree of swelling ^{c)}
1	6.3	2.1	91	300	8	2.70
2		8.2		400	30-36	
3		7.7	95	300	11-12	
4	6.3	8.3		425	28-34	3.05
5		-	94.2	350	16-20	
6	9.5	2.3		500	40	4.75

-13-

- a) 1 = myo-inositol/glycolide/ ϵ -caprolactone-prepolymer +
L-lysine ethyl ester diisocyanate
2 = extracted network 1
3 = precipitated myo-inositol/glycolide/ ϵ -caprolactone
5 prepolymer + L-lysine ethyl ester diisocyanate
4 = extracted network 3
5 = myo-inositol/L-lactide/ ϵ -caprolactone prepolymer +
L-lysine-ethyl ester diisocyanate
6 = extracted network 5
- 10 b) chain length = amount of lactones (L-lactide, glycolide,
 ϵ -caprolactone) per OH group, calculated
from the employed amount of myo-inositol
- c) in chloroform, 20°C.

15

Fig. 1 shows the stress-strain curves for the
glycolide/ ϵ -caprolactone copolyester urethane networks
before (dotted line) and after (solid line) extraction
with chloroform, in the concrete the networks 3 and
20 4 of the Table.

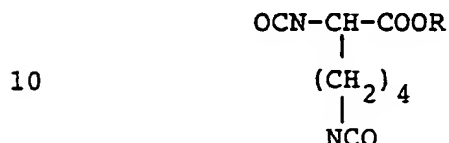
All of the polyurethane networks showed a rubbery
behaviour, and the extracted polyurethane networks showed
superior mechanical properties, a higher elongation
at break and a higher tensile strength (30-40 MPa) when
25 compared with the unextracted networks.

C L A I M S

1. A biodegradable polyurethane on the basis of a polyol prepolymer and a polyisocyanate, characterized in that the polyisocyanate is an L-lysine derivative having at least 2 isocyanate groups.

5 2. A polyurethane according to claim 1, in which the polyol prepolymer is a polyester polyol prepolymer.

3. A polyurethane according to claim 1 or 2, in which the L-lysine derivative satisfies the structural formula

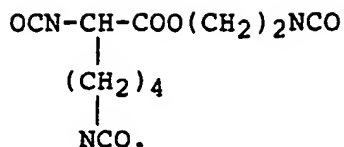


in which R is an alkyl, aryl, alkaryl or aralkyl group, which may be substituted by one or more isocyanate groups and/or groups inert in the polyurethane-forming reaction, such as alkoxy groups.

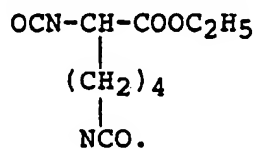
15 4. A polyurethane according to claim 2 or 3, in which the polyester polyol prepolymer is a polyester diol prepolymer and the L-lysine derivative contains at least 3 isocyanate groups.

20 5. A polyurethane according to claim 4, in which the L-lysine derivative is the compound L-lysine aminoethyl ester triisocyanate having the structural formula

-15-



6. A polyurethane according to claim 4 or 5, in which
 5 the polyester diol prepolymer is obtained by a ring-opening polymerization reaction of L-lactide, glycolide and/or one or more lactones, such as ϵ -caprolactone and δ -valerolactone, if desired with a diol.
7. A polyurethane according to claim 4 or 5, in which
 10 the polyester diol prepolymer is obtained by a ring-opening polymerization reaction of L-lactide and/or glycolide with one or more lactones, such as ϵ -caprolactone and δ -valerolactone, and if desired with a diol.
8. A polyurethane according to claim 2 or 3, in which
 15 the polyester polyol prepolymer contains at least 3 hydroxyl groups and the L-lysine derivative is an L-lysine diisocyanate.
9. A polyurethane according to claim 8, in which the
 20 L-lysine derivative is the compound L-lysine ethyl ester diisocyanate having the structural formula



10. A polyurethane according to claim 8 or 9, in which
 25 the polyester polyol prepolymer is obtained by a ring-opening polymerization reaction of L-lactide, glycolide and/or one or more lactones, such as ϵ -caprolactone and δ -valero-

lactone, with a polyol containing at least 3 hydroxyl groups.

11. A polyurethane according to claim 8 or 9, in which the polyester polyol prepolymer is obtained by a ring-opening polymerization reaction of L-lactide and/or glycolide with one or more lactones, such as ϵ -caprolactone and δ -valerolactone, and with a polyol containing at least 3 hydroxyl groups.

12. A polyurethane according to claim 10 or 11, in which the polyol is a cyclic polyol having at least 3 hydroxyl groups.

13. A polyurethane according to claim 12, in which the cyclic polyol is myo-inositol.

14. A polyurethane according to claim 1, in which the polyol prepolymer is a polyester polyol prepolymer, obtained by a ring-opening polymerization reaction of L-lactide or glycolide with ϵ -caprolactone and with myo-inositol, and the L-lysine polyisocyanate is the compound L-lysine ethyl ester diisocyanate.

15. A polyurethane according to any of the preceding claims consisting of a porous network.

16. A polyurethane according to claim 15, obtainable by carrying out the reaction between polyester polyol prepolymer and L-lysine polyisocyanate in the presence of a salt, such as sodium chloride, and removing this salt later, e.g., by treatment with water, whereby pores remain.

-17-

17. A polyurethane according to any of the preceding claims, which comprises precipitating the polyester polyol prepolymer by means of a non-solvent, such as ethanol, from a solution of the prepolymer in an organic solvent, such as chloroform.

18. Products, completely or partly consisting of a polyurethane according to any of the preceding claims.

19. Sheet-like biomedical products, such as artificial skin, wound dressing, etc. and tubular biomedical products, such as artificial veins, vein grafts, nerve grafts etc., completely or partly consisting of a polyurethane according to any of claims 1-17.

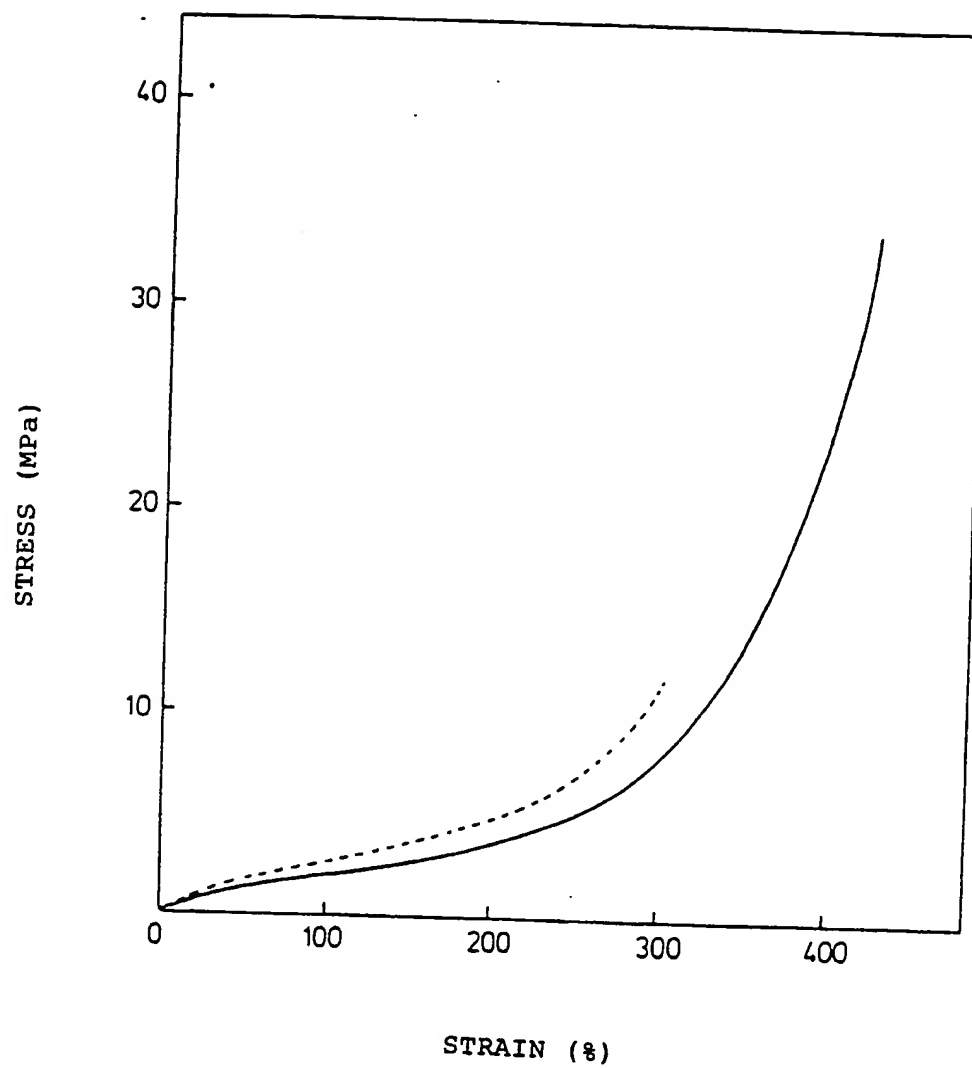
20. Biomedical products according to claim 19, comprising one or more layers of a porous polyether urethane as well as one or more layers of a polyurethane according to any of claims 1-17.

21. A polyester polyol prepolymer on the basis of (1) a cyclic polyhydroxy compound having at least 3 functional hydroxyl groups, (2) L-lactide and/or glycolide, and (3) one or more lactones, such as ϵ -caprolactone and δ -valerolactone.

22. A polyester polyol prepolymer according to claim 21, in which the cyclic polyhydroxy compound is myo-inositol.

23. A polyester polyol prepolymer according to claim 21 or 22, in which the lactone is ϵ -caprolactone.

1/1



INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 88/00060

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁴ : C 08 G 18/77; A 61 L 15/01; A 61 L 27/00; A 61 F 2/06		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁴	C 08 G; A 61 L; C 08 J	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	US, A, 3358005 (J.D. GARBER et al.) 12 December 1967, see column 1, lines 16-46; examples 2,12 --	1-3,18
X	US, A, 4247675 (T. FUKUDA et al.) 27 January 1981, see claims 1-5; column 3, lines 14-20; column 4, lines 52-59 --	1,4,5,18
A	Journal of Polymer Science, Part A - Polymer Chemistry, vol. 25, no. 4, April 1987, John Wiley & Sons, Inc. (New York, US) C.G. Pitt et al.: "The synthesis of biodegradable polymers with functional side chains", pages 955-966, see abstract (cited in the application) --	8,10
A	US, A, 3663515 (F. HOSTETTLER et al.) 16 May 1972, see claims 1,5 --	6
A	US, A, 3882054 (F. HOSTETTLER et al.) 6 May 1975, see claims 1-3,5; column 3, lines 16-53; column 4, lines 8-15 --	16
<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
22nd March 1989	12. 04. 89	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	GB, A, 2127839 (ETHICON INC.) 18 April 1984, see claim 1	21
	--	
A	US, A, 4057537 (R.G. SINCLAIR) 8 November 1977, see claim 1	21

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

NL 8800060
SA 25961

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 05/04/89. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3358005		NL-A- 6515244	25-05-66
		CH-A- 482761	15-12-69
		DE-A- 1595012	05-03-70
		CH-A- 496045	15-09-70
		CH-A- 517135	31-12-71
		GB-A- 1138205	
		FR-A- 1466389	
US-A- 4247675	27-01-81	None	
US-A- 3663515	16-05-72	DE-A- 1914087	09-07-70
		FR-A- 2004564	28-11-69
		GB-A- 1272094	26-04-72
		DE-A- 1966169	18-11-71
		DE-A- 1966170	18-11-71
		GB-A- 1273520	10-05-72
		BE-A- 730261	01-09-69
		DE-A- 1966923	15-05-75
		CA-A- 943293	05-03-74
US-A- 3882054	06-05-75	None	
GB-A- 2127839	18-04-84	AU-A- 1979583	05-04-84
		DE-A- 3335588	05-04-84
		JP-A- 59082865	14-05-84
		US-A- 4605730	12-08-86
		CA-A- 1224600	21-07-87
		US-A- 4700704	20-10-87
US-A- 4057537	08-11-77	None	

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.